B1 Sub D1 a plurality of discrete capture zones on said surface, each said capture zone comprising receptors immobilized thereon capable of binding one or more of said plurality of target ligands.

REMARKS

The invention relates in part to immunoassay devices comprising elements for the controlled flow, delivery, incubation, separation, washing and other steps of the assay process. The devices of the present invention can provide advantageous capture efficiencies and sensitivities for the assay of plurality of target molecules.

Claims 74-91 are presently pending in the instant application, and Claim 74 has been amended herein. The amended claim is commensurate in scope with the claim as filed, and is offered solely to assist the Examiner in understanding the claimed invention. No new matter is introduced.

Notwithstanding the foregoing, Applicant expressly reserves the right to pursue subject matter no longer claimed in the instant application in one or more applications which may claim priority hereto. Applicant respectfully requests reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

Non Art-Based Remarks

35 U.S.C. § 112, Second Paragraph

Applicant respectfully traverses the rejection of claims 74-84 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particular point out and distinctly claim the subject matter which applicant regards as the invention.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.") (emphasis added).

Applicant respectfully submits that the Examiner's assertion that Claim 74, lines 3-4, may be confusing because "if the surface is smooth, then it will not have the protrusions" misinterprets the language of the claims. Claim 74 refers to "a nonporous smooth surface or a nonporous textured surface comprising one or more depressions and/or protrusions." One skilled in the art would reasonably understand that the depressions or protrusions referred to in claim 74 refer to the alternative in which the surface is textured surface. Nevertheless, in an effort to advance prosecution, Applicant has amended the claim to explicitly recite that it is the nonporous surface that comprises one or more depressions or protrusions. Applicants respectfully submit that this amendment renders the rejection moot.

Art-Based Remarks

35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 74-91 under 35 U.S.C. §102 (b), as allegedly being anticipated by Grenner et al., U.S. Patents 5,051,237 ("the '237 patent").

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. Furthermore, the claims must be interpreted in light of the teaching of the specification. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). See also MPEP §2131.

The instant claims relate to assay devices for detecting a plurality of target ligands in a sample. The claimed assay devices comprise a nonporous smooth surface or a nonporous textured surface, comprising a plurality of discrete capture zones on these surfaces, each of which comprises immobilized receptors capable of binding one or more of the plurality of target ligands of interest.

In a related application (09/805,653), the Examiner has taken the position that the phrase "a plurality of target ligands" does not refer to different ligands, and that this phrase might refer to a number of molecules of the same ligand. Applicant respectfully submits that this is not a reasonable interpretation of the phrase. The skilled artisan would understand that a "target ligand" is an analyte - one particular molecular species, which may exist as many molecules of the same species - detected in an assay. A "plurality of target ligands" refers to two or more different molecular species that are detected in an assay, and not two or more molecules of a

single ligand. Applicant also notes that a patentee is free to be his or her own lexicographer, so long as that meaning is made clear in the specification or file history. *See*, MPEP § 2173.05(a).

Applicant respectfully submits that when the instant claims are properly interpreted, the '237 patent fails to disclose any such devices. The Examiner refers to "an assay device having projections (22) and a plurality of discrete reaction zones" (Paper No. 10, page 2), but does not indicate how such projections or reaction zones might be interpreted as discrete capture zones for binding to a plurality of target ligands.

Moreover, the projections (22) of the '237 patent are said to provide "controlled flow of fluid," rather than any structure related to discrete capture zones. Applicants cannot identify any reference in the '237 patent to "a plurality of discrete reaction zones" as the Examiner contends, and respectfully requests that the Examiner indicate where such a disclosure may be found in the cited publication. The '237 patent refers to a diagnostic assay element for determining a single analyte. *See, e.g.*, '237 patent, column 6, lines 24-26 ("In one embodiment reagent layer 30 comprises an immunocomplex of a fluorescent-labeled antigen and an antibody directed against the antigen" (emphasis added)).

Therefore, because the '237 patent does not disclose every limitation of the claimed invention, the claims in the instant application, no *prima facie* case of anticipation has been established. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be reconsidered and withdrawn.

35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 74-91 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Watts *et al.*, U.S. Patent No. 5,437,983 ("the '983 patent") or Sutton *et al.*, U.S. Patent No. 5,888,723 ("the '723 patent").

To establish a *prima facie* case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to the ordinarily skilled artisan, to modify or combine the references; there must be a reasonable

expectation of success in combining the references; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) *See also,* MPEP §2143.

The instant claims refer to assay devices comprising a plurality of discrete capture zones on the surfaces for determining one or more of a plurality of target ligands of interest. The Examiner contends that each of the cited patents disclose the use of beads that correspond to a surface comprising a plurality of discrete capture zones for determining a plurality of target lignds, and that it is only the dimensions of the depressions and/or protrusions that are not disclosed. Applicants respectfully disagree.

With regard to the '983 patent, nothing in the cited patent discloses a single surface having a plurality of discrete capture zones, each of which comprises immobilized receptors capable of binding one or more of a plurality of target ligands of interest. Rather, the '983 patent discloses the use of beads having specific binding pair members for a single analyte affixed to their surface. Even when a plurality of such beads are used, the '983 patent uses such beads for determining a single analyte. *See, e.g.*, '983 patent, column 8, lines 52-59. No single bead is indicated to have a plurality of discrete capture zones, and no surface comprises beads immobilized in discrete zones so that a plurality of analytes may be detected. Therefore, the '983 patent does not teach or suggest each and every limitation of the present invention.

Similarly, the '723 patent also discloses the use of beads having specific binding pair members for a single analyte affixed to their surface. Again, No single bead is indicated to have a plurality of discrete capture zones, and no surface comprises beads immobilized in discrete zones so that a plurality of analytes may be detected.

Applicant also respectfully submits that the '723 patent, cited presumably as allegedly being 102(e) art based on a priority date of February 18, 1992, is not prior art to the instant application. In support of this fact, Applicant submits herewith the declaration of Kenneth Buechler, the inventor of the presently claimed invention. In this declaration, Dr. Buechler indicates that the claimed invention, i.e., assay devices comprising a nonporous surface, and a plurality of discrete capture zones on the nonporous surface, were invented by Applicant prior to the filing date of the '723 patent.

Because none of the publications disclose or suggest the instantly claimed invention, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness, and respectfully requests that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicant respectfully submits that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

FOLEY & LARDNER

Dated: September 13, 2002

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Appendix A: A mark-up version of amended claim, indicating the change.

74 (Amended). An assay device for detecting a plurality of target ligands in a sample, comprising:

a nonporous smooth surface or a nonporous textured surface, said nonporous textured surface comprising one or more depressions or protrusions extending between 1 nm and 0.5 mm from said nonporous textured surface; and

a plurality of discrete capture zones on said surface, each said capture zone comprising receptors immobilized thereon capable of binding one or more of said plurality of target ligands.

D. Lawrence #13 9/24/02

Atty. Dkt. No. 071040-1307
Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kenneth F. Buechler

Serial No.: 09/613,650

Filed: July 10, 2000

For: **DIAGNOSTIC DEVICES AND APPARATUS FOR THE CONTROLLED MOVEMENT OF REAGENTS WITHOUT MEMBRANES**

Group Art Unit: 1743

Examiner: Alexander, Lyle

CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date below.

Jodie Rivas
(Printed Name)

(Signature)

9/13/02
(Date of Deposit)

DECLARATION OF KENNETH F. BUECHLER

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Kenneth F. Buechler, declare that:

1. I earned a Ph.D. in 1981 from the Department of Biochemistry, Indiana University . I have been engaged in research involving diagnostic assays for 17 years. A copy of my curriculum vitae is attached hereto as Appendix A. I am currently employed as Vice President, Research and Development, at BIOSITE, Inc., 11030 Roselle Street, San Diego, CA 92121.

2. I have reviewed the instant patent application, and I am familiar with the assay devices described therein. I hereby certify that the copies of notebook pages attached hereto as Appendices B and C and referred to below are true and accurate copies.

3. I described the initial concept for an assay device comprising a non-porous surface, and a plurality of discrete capture zones on the non-porous surface, prior to February 18, 1992. A copy of two pages from my laboratory notebook written before that date and describing such a device is attached hereto as Appendix B. As noted on the page labeled "94," lower right corner, the basic device uses "a solid, non-porous...surface." The drawing on the lower left corner notes that the receptors ("Ab" for "antibody") may be located on the surface in "spots or bars."

4. Prior to February 18, 1992, this conception had matured into the devices depicted in the figures submitted with the present application. For example, an additional page from my laboratory notebook written before that date, attached hereto as Appendix C, depicts an assay device that is substantially equivalent to the drawing of the claimed devices in Fig. 1 of the present application. This drawing depicts diagnostic lane "f," and notes that one or more reagents for immobilization are placed here for "one or multiple analyte detection."

5. The concept of a non-porous surface, and a plurality of discrete capture zones on the non-porous surface, was then made the subject of the present application. This application was drafted and submitted to the U.S. Patent and Trademark on May 21, 1992.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001 of Capital Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Sept 9, 2002
Date

Kenneth F. Buechler
Dr. Kenneth F. Buechler

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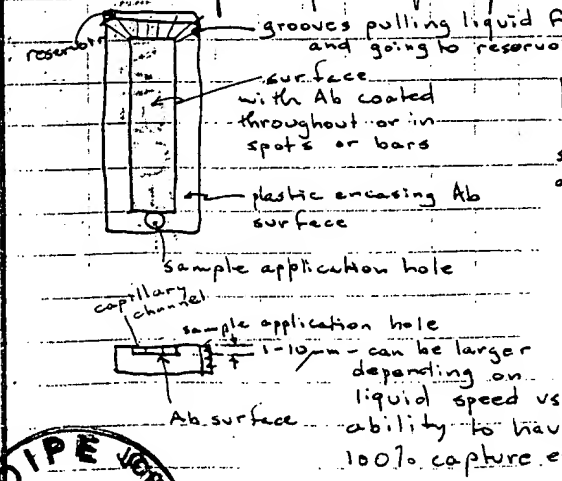
PURPOSE: The purpose here is to describe an assay device which uses a surface to immobilize the Ab rather than a membrane. The reason to use a surface is that one can control flow more easily through a capillary channel(s) than through a membrane. We have always had problems with membranes, their heterogeneity.

DESCRIPTION: First a description of a device where a surface is utilized will be discussed. Then, using what I would call a hybrid between a surface and a membrane device, a "rough surface" will be considered.

The device is considered as the following: A surface on which Ab (for example) is immobilized is incorporated on a base and a top cover is placed over this Ab surface such that a capillary gap separates the Ab surface and the top cover. This gap allows liquid to move through it spontaneously via capillary action. The gap can be adjusted to alter the flow of liquid, both speed and direction, so that control of liquid flow is established by the use of capillary force. Also, the gap should be small 1-10 μm such that diffusion is rapid from the bulk solution to the membrane surface. Sample would be applied to one end of the capillary gap and it would run down the gap. Analyte would bind to the surface (ie., labelled conjugate) and the responses measured. An example of a proposed device is the following:



This basic device can be used with many different Ab surfaces. It is these surfaces which is the key to the success of the device. Immobilization of high amounts of Ab on a solid, non-porous or just semi-porous surface is needed to drive the reaction on the surface

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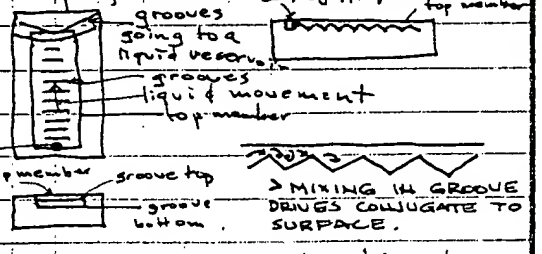
The Ab surface could also be a grooved surface such that the Ab is immobilized within the grooves. Using a grooved surface would allow a controlled flow of liquid through the device, thus obviating the problem with poor flow through a membrane.

One could also increase the surface area of the surface by immobilizing, for example, a mono layer of microspheres or by embossing the surface. The application of the microspheres (10 - 100 μm) which would have Ab already bound would allow then the placement of the top part of the device directly on the microspheres. The capillary action of the liquid would go through force the liquid through the device. A slight capillary space could also be present depending on the capillary force needed to pull the liquid by the surface.

The kinds to immobilize the Ab to the surface could involve direct adsorption, chemical attachment via maleimide or NHS-esters on the surface, or preparing an Ab polymer backbone (i.e., attaching Ab's to soluble polymers using NHS-esters of maleimides of polymers and subsequently immobilizing the polymer on the surface.

Placing the Ab on a grooved surface (grooves ~10 μm for example) and placing a top member just above the top of the groove (eg. ~1 - 20 μm) and allowing the movement of sample + conjugate to move in a direction 90° to the groove length would cause a mixing of the conjugate / sample as it went up the device. Furthermore, as the sample went from the groove bottom to the groove top it would tend to confine itself to a small gap since the top member is very near the groove top. This could cause an actual driving force for placing the conjugate to bind to the Ab at the tip of the groove. Again, capillary action drives the liquid up the grooves. Having the grooves 90° to the liquid front also causes a uniform front up the device. This hypothesis To Page No. tested with a membrane.



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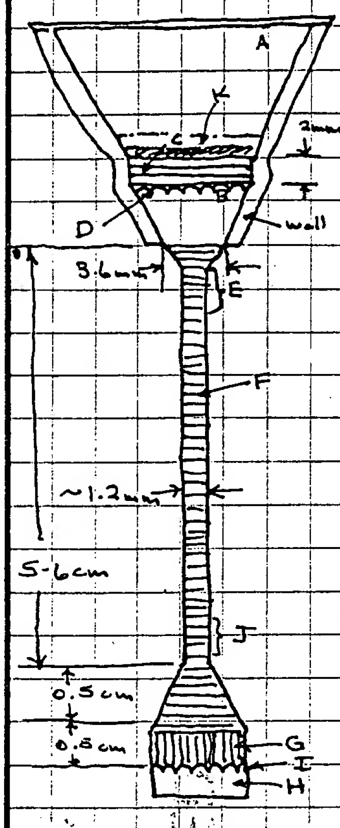
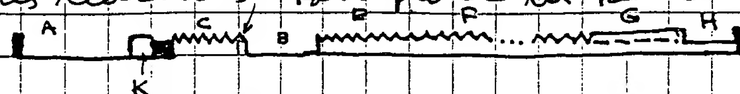
Various aspects of the one-step device have been worked on and here I will assemble them into the whole. The picture below is the bottom part of the device. A clear top-piece is placed on top of this to create the sample and reaction volumes, but the top piece is not drawn.



Sample is applied at A & moves to H via capillary forces. Various reactions take place in between!



A = represents the sample addition reservoir. Here a prefilter can be placed. The dimensions are such that ~ 150-200µl fills this volume. This is where sample is placed.

B = reaction chamber. This for now is for 50µl. This volume = 50µl. Reagents for the assay are placed here.

C = grooved surface - This separates the sample addition reservoir and the reaction chamber.

D = fingers. These act as a capillary means to cause the liquid to move into the reaction chamber. Dimensions are, for now, 0.040" 0.016" ← 10 fingers

E = time gate goes here. Grooved surface but can ~~Fe~~ be flat here also. Grooves may be better for drying the latex.

F = diagnostic lane and/or place for the optional means reagents. Grooves are ______. The capture phase is here so reagents used for the capture are immobilized here.

G = These grooves run perpendicular to the diagnostic lane grooves. These grooves pull the reagents from the diagnostic lane. They have a higher capillary pull, ideally, than the diagnostic lane. The reagents for immobilization of label are here. One or more reagents immobilized for one or multiple analyte detection.

H = Used reagent reservoir. The reagents go here. An absorbant material may be used in here to absorb the reagents.

I = fingers = serve to cause flow to go into used reagent reservoir.

J = zone for showing reaction or assay is complete. Reagents here bind the label to show the assay is complete.

K = filter element - in ~~sample~~ addition reservoir. Top of filter is in contact of lid. A capillary space after the filter gives sample to "C".

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